Detecting Early Stage Cancer using Liquid Biopsy

Jackie Baek Vivek Farias Chinmay Jha Andrew Li **Deeksha Sinha**
MIT

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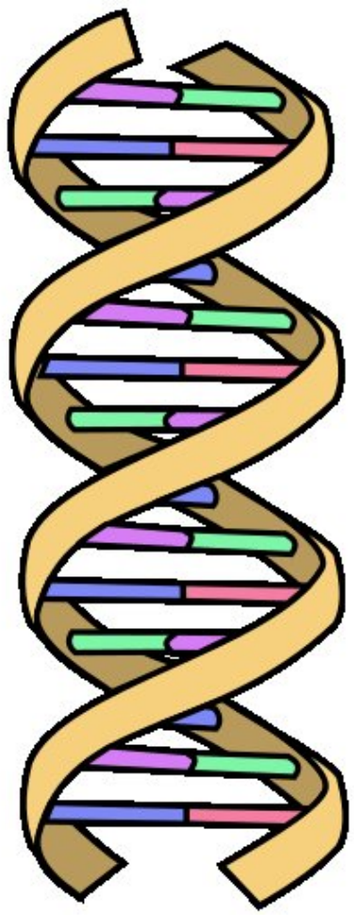
  - Fueled by tremendous reductions in DNA sequencing cost
- **Goal:** develop a cost-efficient liquid biopsy to detect early-stage cancer

Biology 101



DNA

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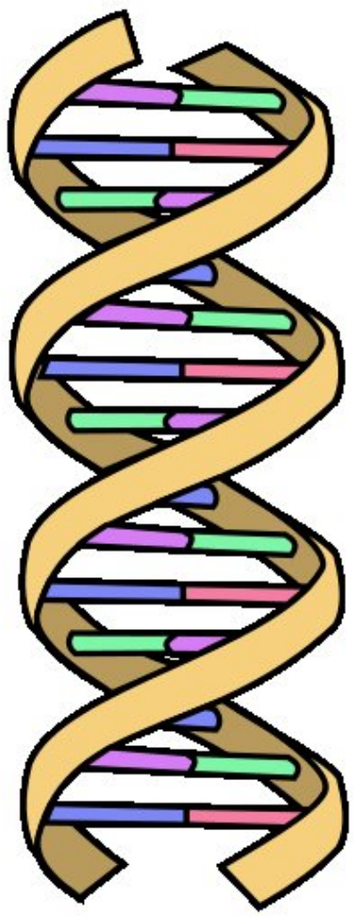

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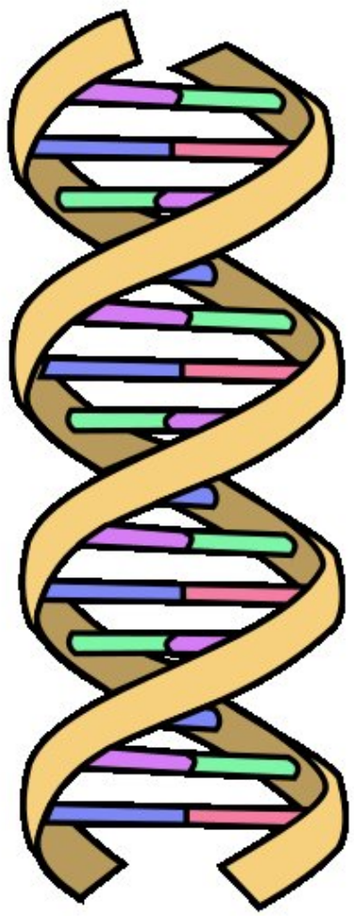

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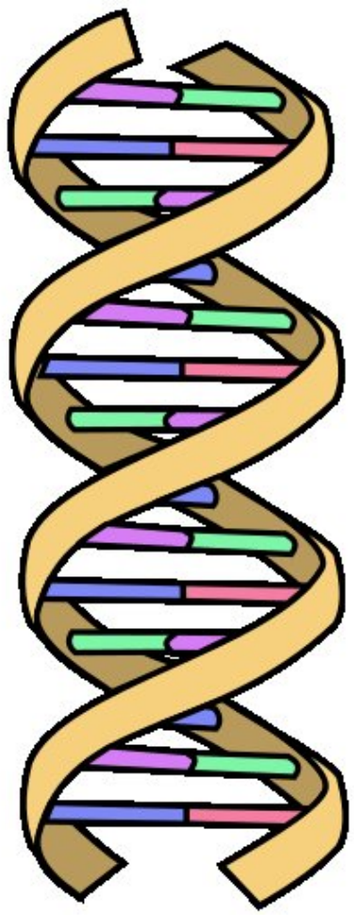

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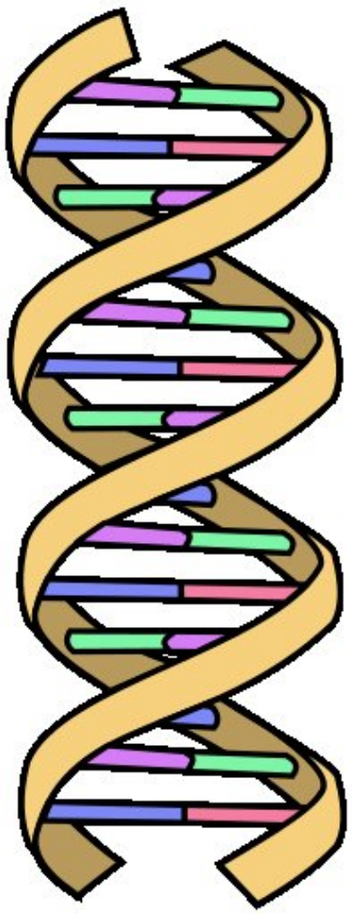

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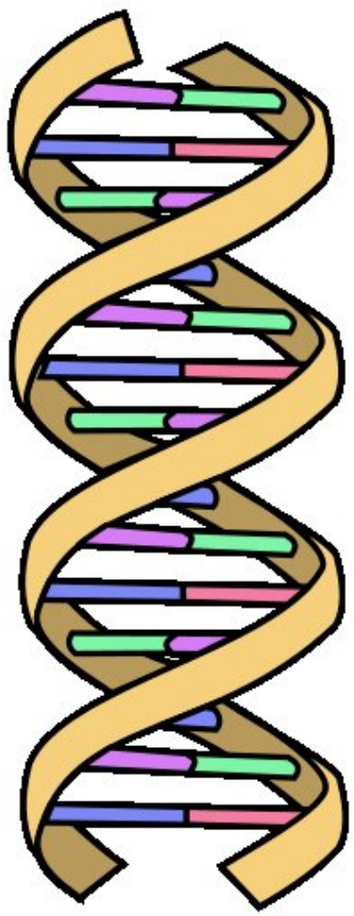

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...ATGC...

...ATGAC...

insertion

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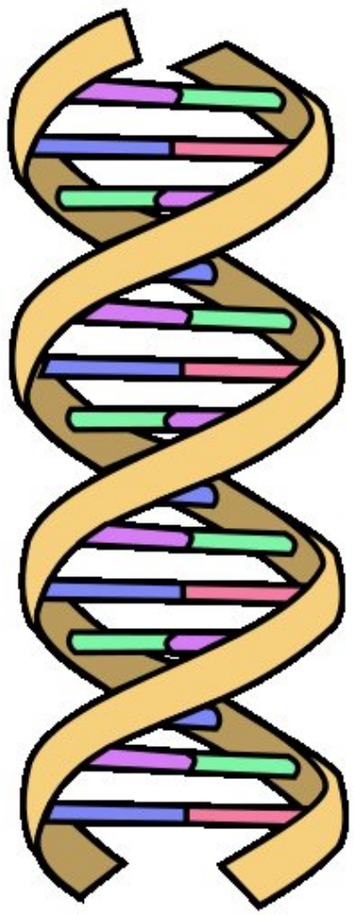

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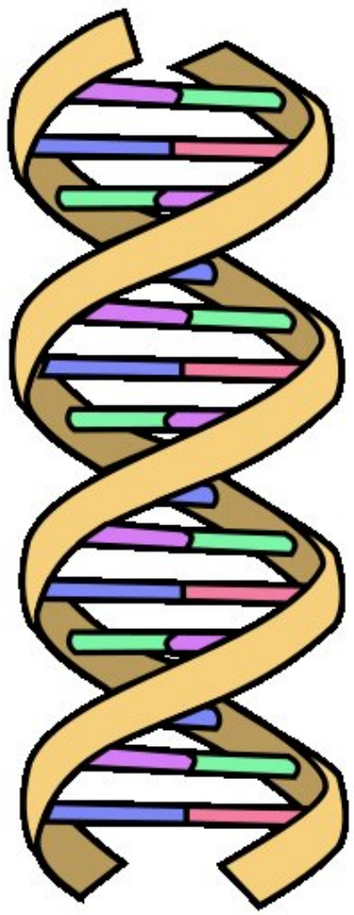

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- **Cancer** is caused by mutations that cause abnormal cell growth
- **Sequencing** is the process of recovering the DNA string

Detecting Early-Stage Cancer

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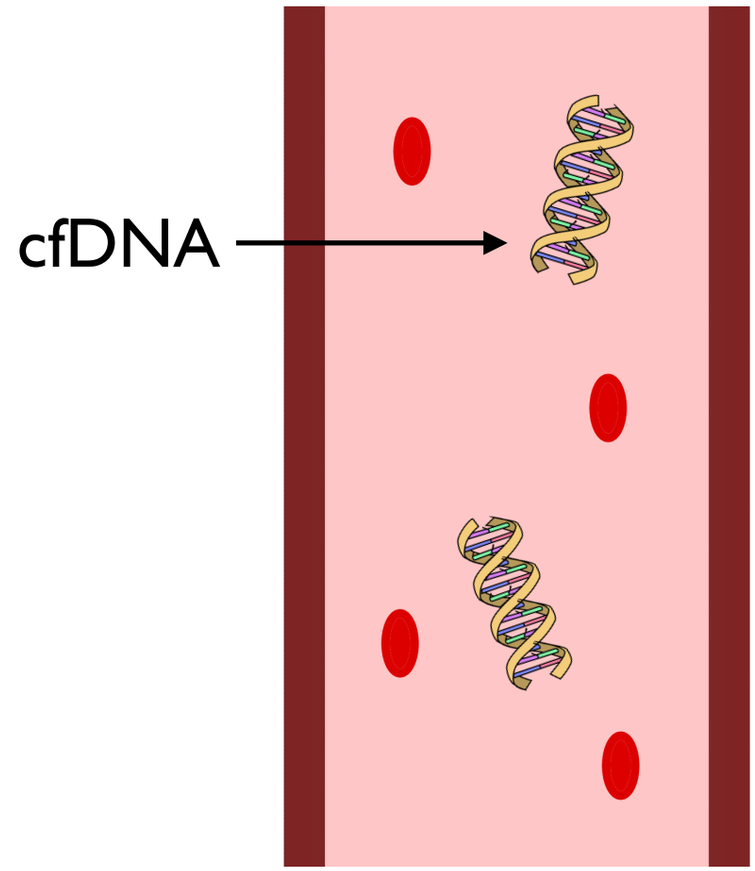
- **Cell-free DNA (cfDNA):** DNA that flows freely in the blood



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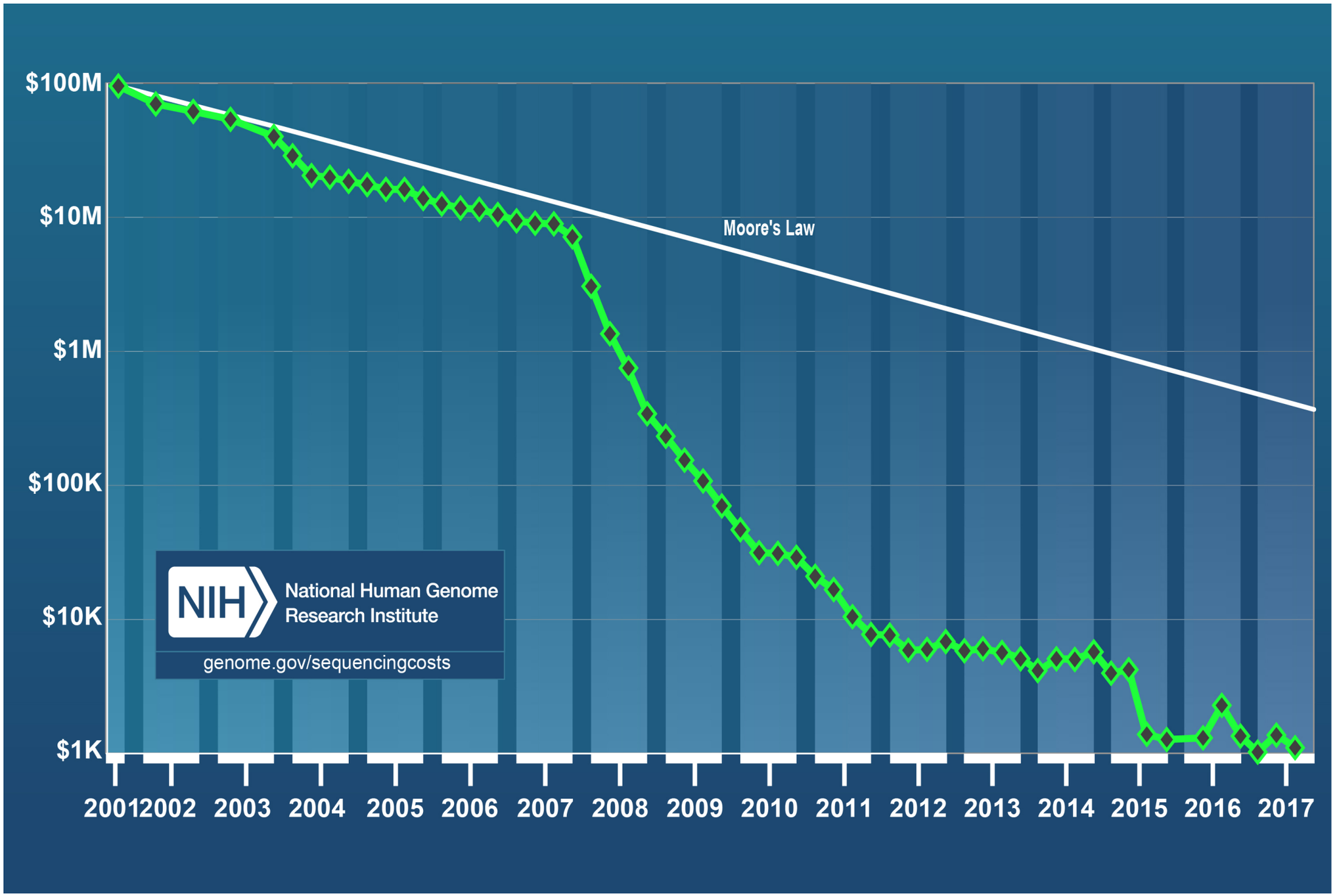
Cost of Sequencing a Human Genome



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AmpliSeq™ for Illumina Cancer Hotspot Panel v2

Fast, accurate investigation of hotspot regions in 50 genes with known cancer associations.

Highlights

- **Relevant Gene Content**
  Target ~2800 COSMIC mutations from 50 oncogenes and tumor suppressor genes
- **Fast, Streamlined Workflow**
  Prepare sequencing-ready libraries in a single day from as little as 1 ng high-quality DNA or 10 ng DNA from FFPE tissue
- **Accurate Data**
  Detect somatic mutations down to 5% frequency using local or cloud-based analysis

Introduction

The AmpliSeq for Illumina Cancer Hotspot Panel v2 is a targeted resequencing assay for researching somatic mutations across the hotspot regions of 50 genes with known associations to cancer

Table 1: AmpliSeq for Illumina Cancer Hotspot Panel v2

Parameter	Specification
No. of Genes	50
Targets	Hotspot regions within oncogenes and tumor suppressor genes
Cumulative Target Size	22 kb
Variant Types	SNVs, indels[a]
Amplicon Size	106 bp on average
No. of Amplicons	207
Input DNA Requirement	1–100 ng (10 ng recommended)
No. of Pools per Panel	1
Supported Sample Types	FFPE tissue, blood
Percent Targets Covered at Minimum 500× at Recommended Throughput	> 95%
Coverage Uniformity (percent of targets with > 0.2× mean coverage)	> 95%
Percent On-Target Aligned Reads	> 80%
Total Assay Time	5 hours[b]

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Which parts of the DNA should be sequenced to detect cancer and classify its type at the lowest possible cost?

Model

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Data

Model

Data

COSMIC database: genome-wide mutation data from cancer patients

$$X = \overbrace{\begin{bmatrix} 0 & 1 & 0 & 0 & \dots & 1 \\ 0 & 1 & 0 & 0 & \dots & 0 \\ 1 & 0 & 0 & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 1 & 0 & \dots & 0 \end{bmatrix}}^{\text{3 billion}} \Bigg\} \text{25000}$$

$$Y = \begin{bmatrix} \text{liver} \\ \text{stomach} \\ \text{lung} \\ \vdots \\ \text{large intestine} \end{bmatrix}$$

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Challenges

- Extremely sparse: 0.03%
- High-dimensional data with limited samples

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Cost of sequencing = (# of addresses) + 42 x (# intervals)

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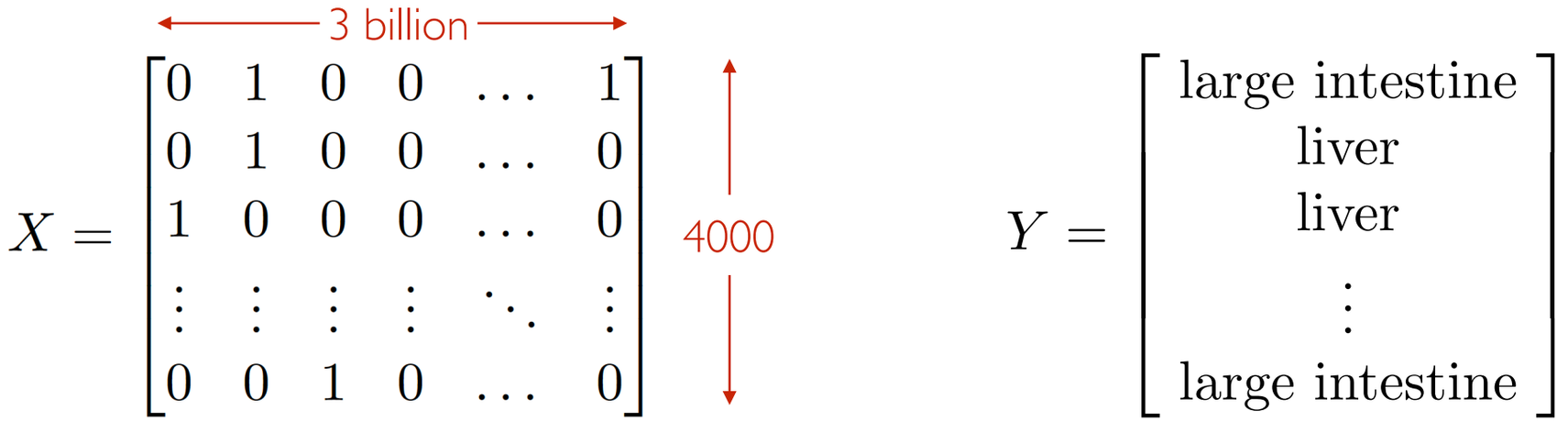

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= (8 + 11) + (42 x 2)

8 11

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Question

Given a cost budget, what is the best classifier?

Classification Model Features

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  - Look for predictive regions in the gene
  - Add features representing a mutation in a **region** in the gene

New features

$$X = \begin{bmatrix} 0 & 1 & 0 & 0 & \dots & 1 \\ 0 & 0 & 1 & 0 & \dots & 1 \\ 1 & 0 & 0 & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 1 & 0 & \dots & 0 \end{bmatrix} \qquad Y = \begin{bmatrix} +1 \\ -1 \\ -1 \\ \vdots \\ +1 \end{bmatrix}$$

$$C = \begin{bmatrix} 43 & 43 & 43 & 43 & \dots & 43 \end{bmatrix}$$

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- Add feature representing a mutation in either of the first two addresses

New features

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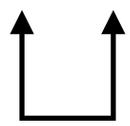

$$C = \begin{bmatrix} 43 & 43 & 43 & 43 & \dots & 43 & 44 \end{bmatrix}$$

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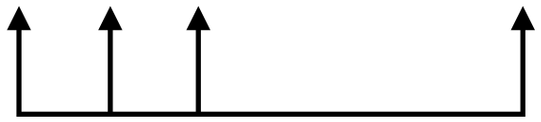

$$Y = \begin{bmatrix} +1 \\ -1 \\ -1 \\ \vdots \\ +1 \end{bmatrix}$$

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- Add feature representing a mutation in either the first, second, third or the last address

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$$X = \begin{bmatrix} 0 & 1 & 0 & 0 & \dots & 1 & 1 & 1 & \dots \\ 0 & 0 & 1 & 0 & \dots & 1 & 0 & 1 & \dots \\ 1 & 0 & 1 & 0 & \dots & 0 & 1 & 1 & \dots \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots \\ 0 & 0 & 1 & 0 & \dots & 0 & 0 & 1 & \dots \end{bmatrix} \qquad Y = \begin{bmatrix} +1 \\ -1 \\ -1 \\ \vdots \\ +1 \end{bmatrix}$$

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- Add features corresponding to all subsets of addresses within a gene
- Exponential increase in number of features

CSVM

$$\min_{\theta} \sum_{i=1}^{m} \mathbf{I}\{f_\theta(x_i) \neq y_i\}$$

$$\text{s.t. cost of classifier} \leq \text{budget}$$

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$$\min_{a,b} \sum_{i=1}^{m} [1 - y_i(a^T x_i + b)]^+$$

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Challenging optimization problem because of large number of features

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- Decompose optimization problem over genes

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- Focus on the inner maximization problem and then solve it over all the genes

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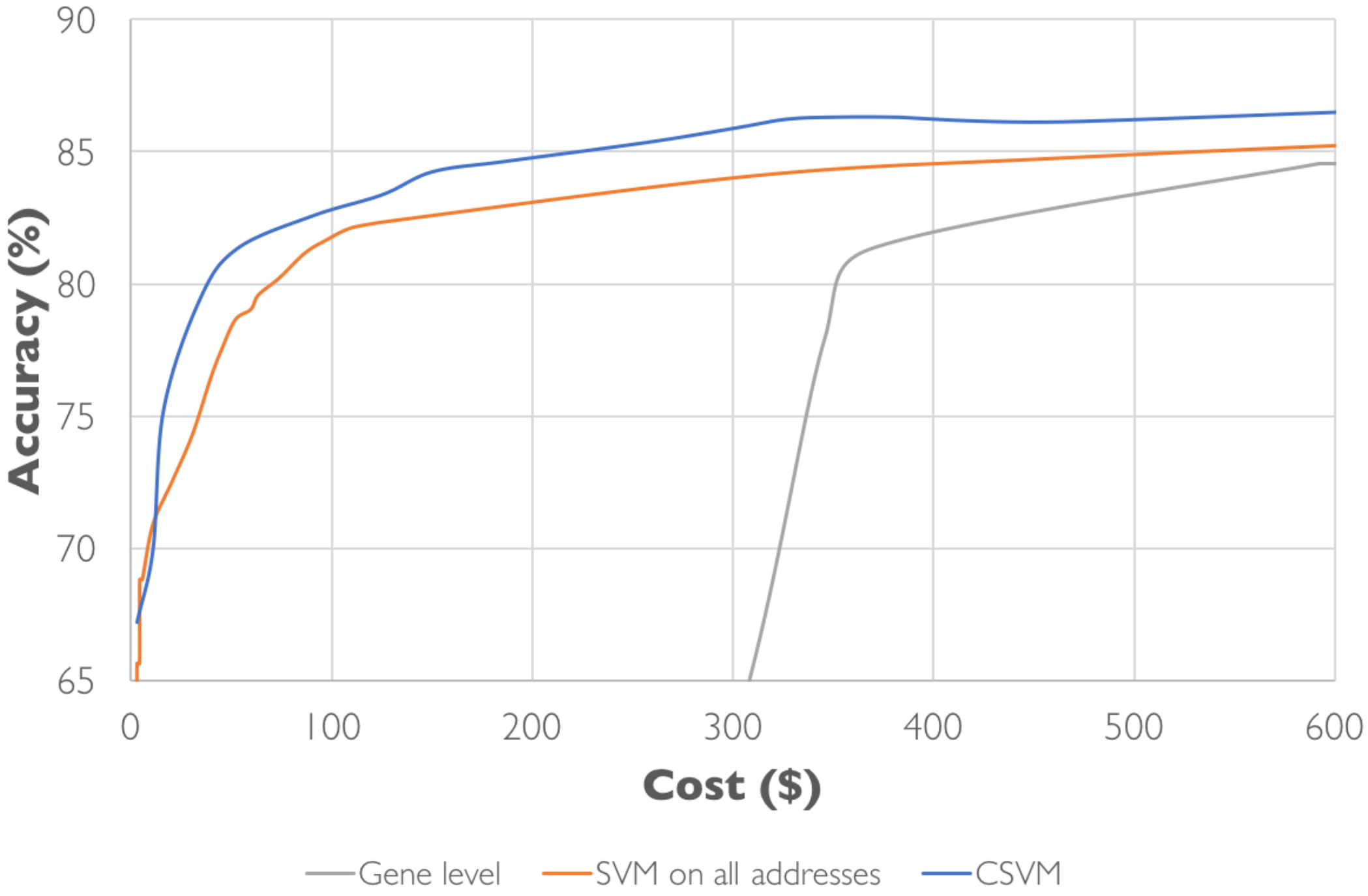
Performance



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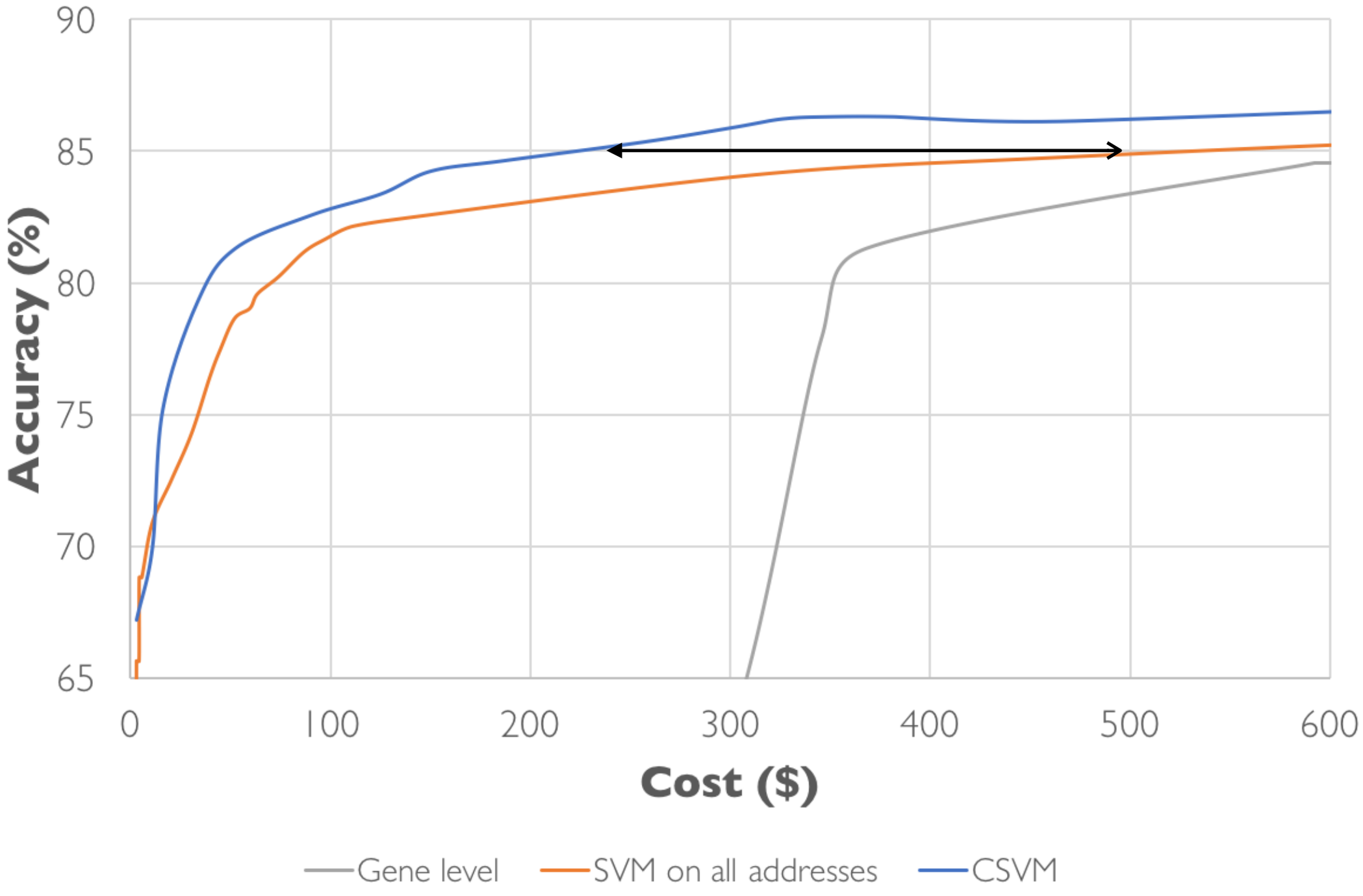
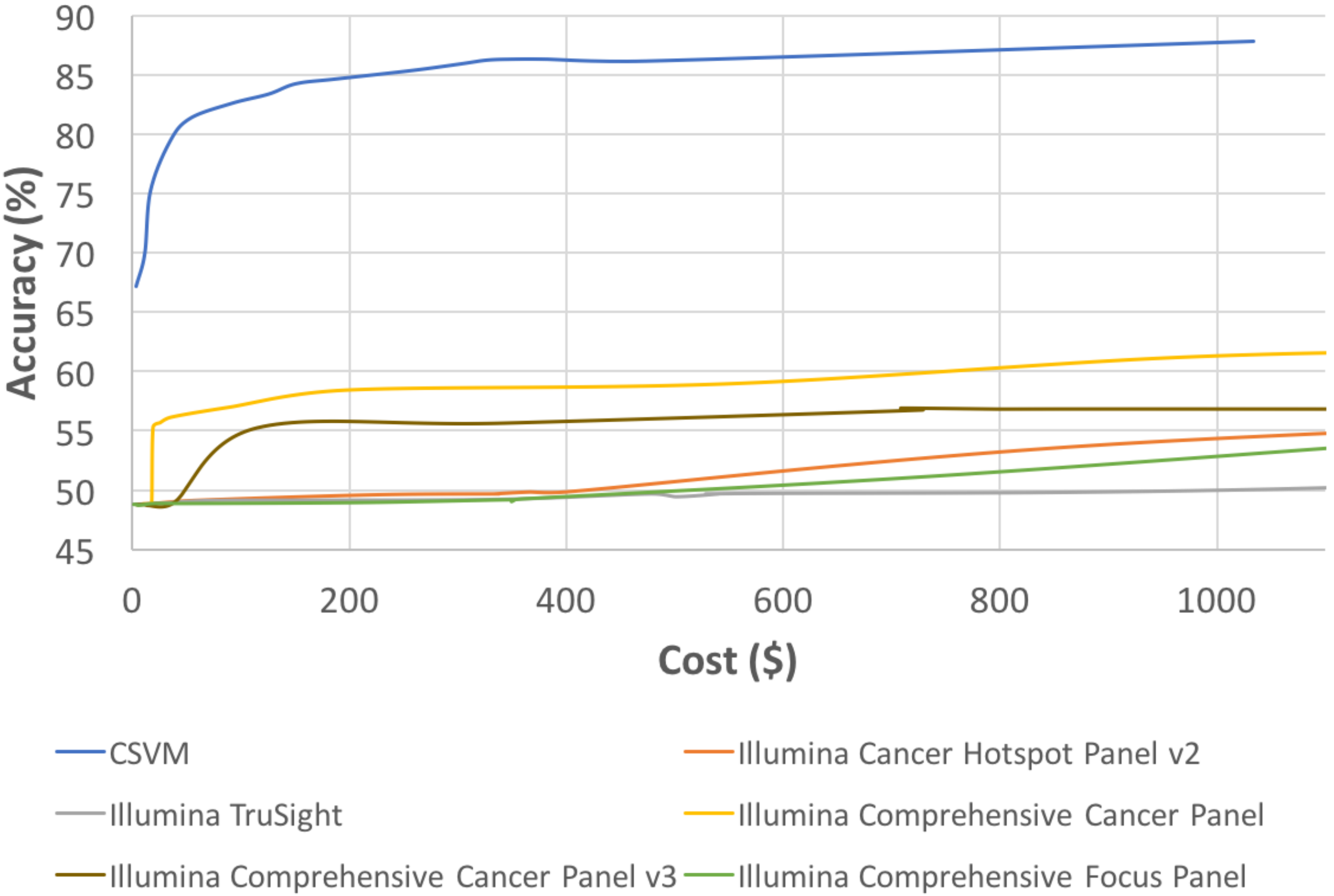


CSVM achieves a $420 cost reduction for attaining accuracy of 85%

Performance



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- Illustrate superior performance of CSVM over benchmark algorithms and existing commercial panels

Thanks!

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i-th sample contains mutations in intervals S_i

It is 'covered' if any of these intervals are chosen

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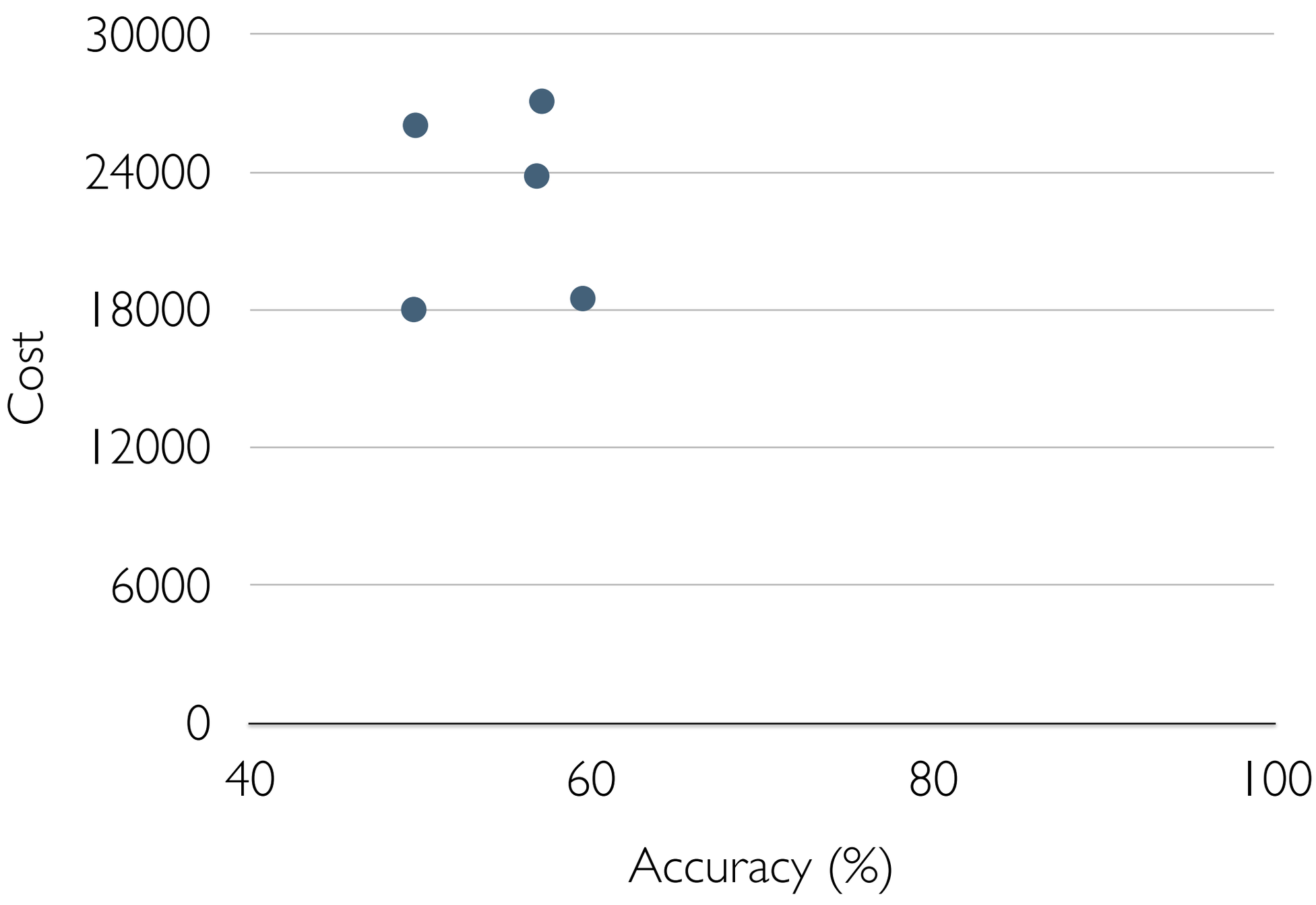
Performance of commercial panels



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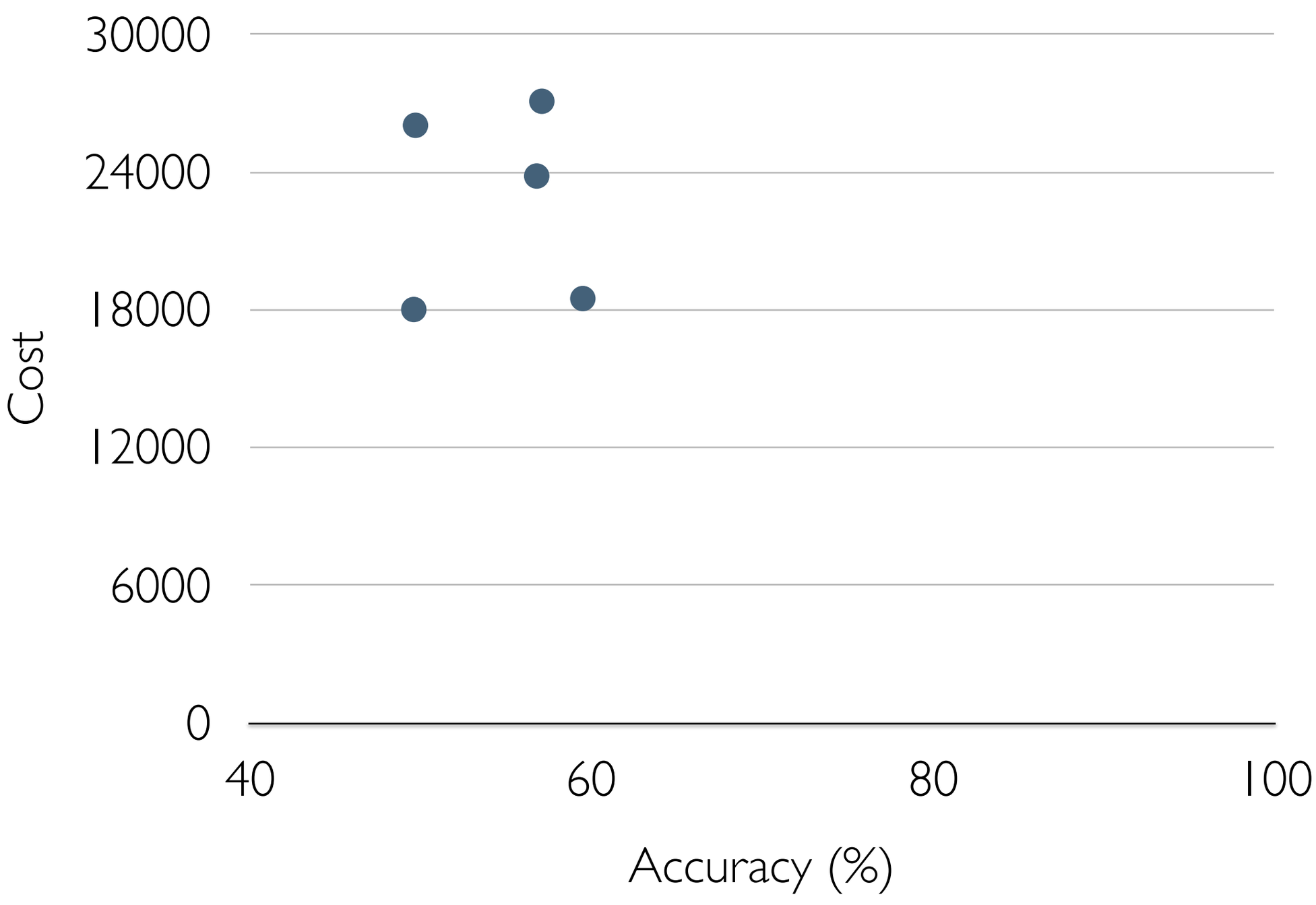

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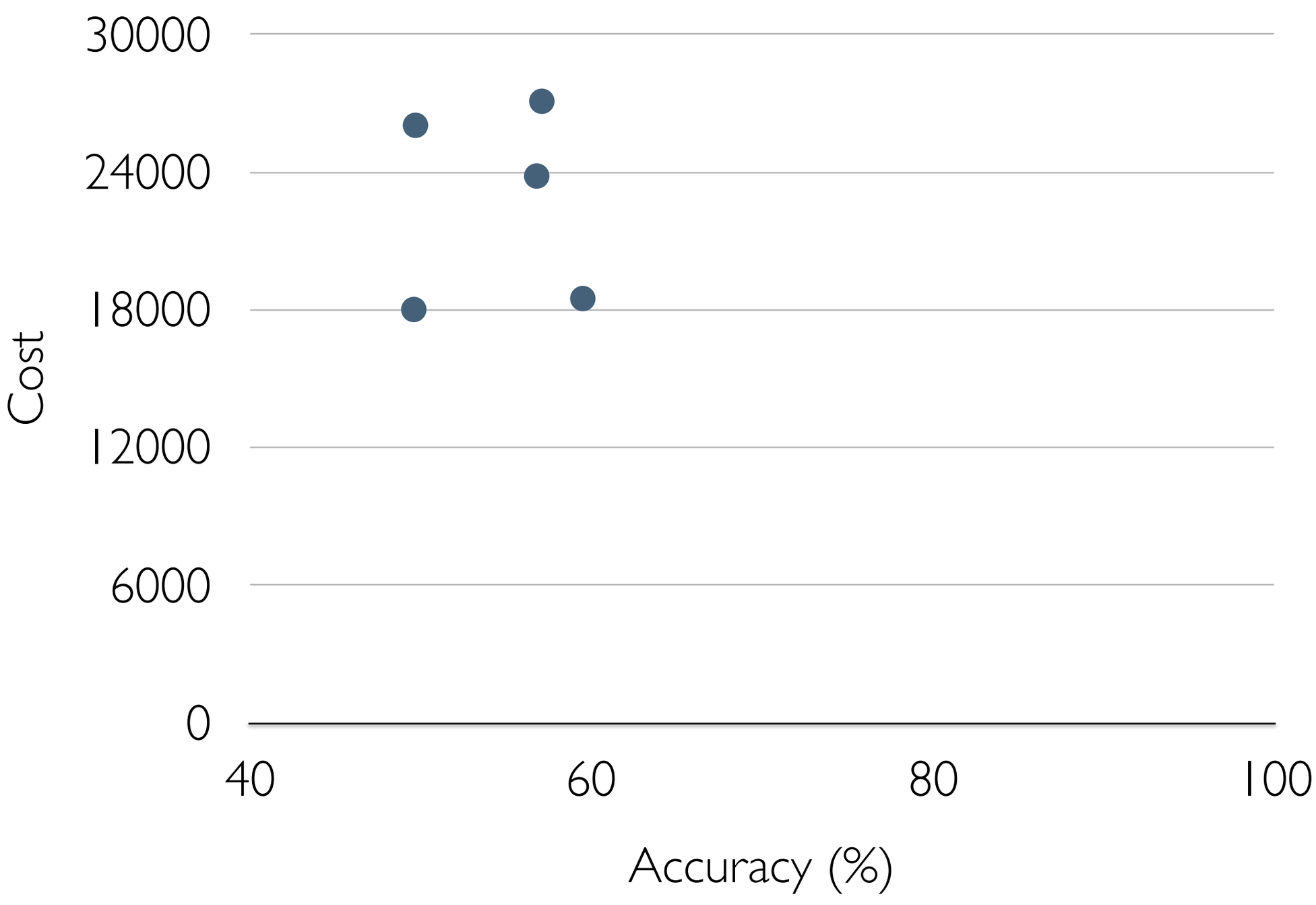

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$$\text{s.t. cost of classifier} \leq \text{budget}$$